(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 203 962 B1**

(12) **EUROPEAN PATENT SPECIFICATION published in accordance with Art. 158(3) EPC**

(45) Date of publication of patent specification: **02.05.91**

(51) Int. Cl.⁵: **A61K 49/00, A61B 5/05, C07F 15/00**

(21) Application number: **85905998.2**

(22) Date of filing: **12.11.85**

(86) International application number: **PCT/US85/02247**

(87) International publication number: **WO 86/02841 (22.05.86 86/11)**

(54) DIAMIDE-DTPA-PARAMAGNETIC CONTRAST AGENTS FOR MR IMAGING, APPARATUS AND METHODS.

(30) Priority: **13.11.84 US 671106**

(43) Date of publication of application: **10.12.86 Bulletin 86/50**

(45) Publication of the grant of the patent: **02.05.91 Bulletin 91/18**

(84) Designated Contracting States: **FR**

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EP 0 203 962 B1

THE JOURNAL OF NUCLEAR MEDICINE, vol. 22, no. 9, September 1981, pages 810-814; D.J. HNATOWICH et al.: "Labeling of preformed liposomes with Ga-67 and Tc-99m by chelation"

CHEMICAL ABSTRACTS, vol. 102, no. 20, 20th May 1985, page 114, abstract no. 168713h, Columbus, Ohio, US; J. MAJER et al.: "Detergents from polyaminopolycarboxylic amides and their salts"

CHEMICAL ABSTRACTS, vol. 105, no. 3, 21st July 1986, page 606, abstract no. 23937m, Columbus, Ohio, US; Y. JIN et al.: "Synthesis of DTPA-bis(N-alkylamide) compounds and their effect on the removal of radionuclides"

SCIENTIFIC AMERICAN, May 1982; I.L. PYKETT: "NMR imaging in medicine"

Description

This invention relates to magnetic resonance imaging (MRI) contrast agents, and more particularly to contrast agents based on chelates of paramagnetic metal species by amides of diethylenetriaminepentaacetic acid (DTPA).

The Journal of Nuclear Medicine 22, 810-814(1981) describes the use of small amounts of monooctadecylamine-DTPA in liposomes to complex the carrier-free radioactive metals Tc-99m and Ga-67 with the intention of improving the state of the art liposome-oxine chelates of these metals in applications in nuclear medicine.

DE-A1-3129906 (Schering/Gries, Rosenberg, and Weinmann) teaches the incorporation of paramagnetic metals into diethylenetriaminepentaacetic acid (DTPA) forming chelates useful as contrast agents in magnetic resonance imaging. The contrast agent DTPA-Gd(III) as taught by Schering is insoluble in water and requires the addition of cations "C+" (amines such as glucamine, N-methylglucamine, etc.) as shown below: The charge balance of the schering DTPA-Gd(III) ion is:

Schering DTPA-Gd(III) Charge Balance

C+	C+	DTPA	Gd	
+1	+1	-5	+3	= 0

The resulting contrast agent has three ion particles in solution for each paramagnetic atom (PM)- a particle to PM ratio of 3:1. A paramagnetic metal with a valence of two, such as Mn, would require an additional glucamine ion:

Schering DTPA-Mn(II) Charge Balance

C+	C+	C+	DTPA	Mn	
+1	+1	+1	-5	+2	= 0

raising the particle to PM ratio to 4:1.

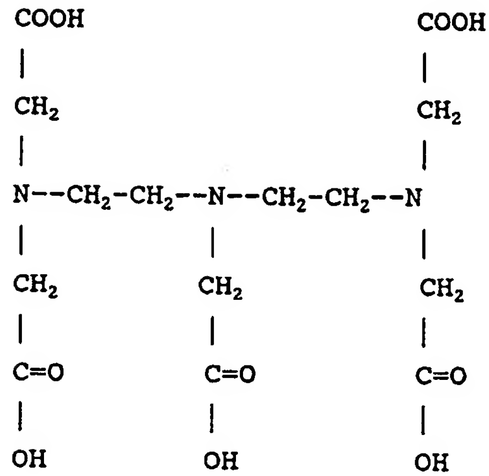
These contrast agents raise the in vivo ion concentration and disturb the local osmolarity balance. The osmolarity is normally regulated at about 300 milliosmols per liter. Increasing the osmolarity with injected ions, causes water to collect within the unbalance region which dilutes the ion concentration.

The present invention is based on the surprising discovery that, by replacing one or more of the carboxy groups of the chelating agent diethylenetriaminepentaacetic acid (DTPA) with amide groups, an improved magnetic resonance imaging contrast agent may be obtained, which has a high stability, low toxicity and is physiologically tolerable.

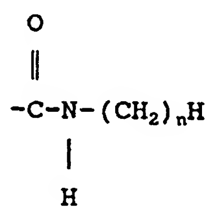
The improved amide contrast agents of the invention may be provided in a pharmacological form having a low osmolarity and are both in vivo responsive and organ selective. Moreover the contrast agents of the invention are particularly useful since they cause surface highlighting of the small and large intestine.

Thus the present invention provides a complex of a paramagnetic polyvalent metal and an amide of diethylenetriaminepentaacetic acid in which the nitrogen of the amide group is unsubstituted or is substituted by at least one C_{1-18} alkyl radical.

This chemically stable physiologically tolerable contrast agent may be provided in a pharmacological state, for in vivo use during diagnostic magnetic resonance (MR) imaging. The contrast agent enhances the MR image of a subject within the MR scanning magnetic field. A paramagnetic metal ion PM(+Z) having an atomic charge of Z locally affects the MR scanning magnetic field to reduce the T1 relaxation time of local protons within the subject. The contrast agent contains a triamine chelator "Amide-DTPA" securely polar bonded around the PM(+Z) ion at a plurality of coordination points, and has the form:



in which at least one, preferably two, of the carboxy groups are replaced by a functional amide group of the form:



wherein "n" is an integer from 0 to 18. This serves to chemically isolate the PM(+Z) ion from the <u>in vivo</u> environment.

The functional amide may be a homo-diamide or a hetero-diamide. The Amide-DTPA-PM contrast agent is dispensed in a pharmaceutically acceptable vehicle means such as water. The carbon-hydrogen portion of the amide compound becomes associated with water of hydration which increases the paramagnetic strength of the contrast agent. The PM ion may have a valence of +3 and produce a contrast agent molecule of zero net charge. The PM ion may have a valence of +2 and require an inert cation IN having an atomic charge to produce a molecule with a zero net charge. The paramagnetic metal ion PM(+Z) is at least one element selected from Transition Elements 24-29 or the Lanthanide Elements 57-71.

The invention is further illustrated with reference to the accompanying drawings in which:

Figure 1A is a diagram showing the chelate structure and water of hydration of a Diamide-DTPA-PM(Z) contrast agent in which Z = +3;

Figure 1B is a diagram showing the chemical structure of the Diamide-DTPA-PM contrast agent of Figure 1A;

Figure 1C is a diagram showing the chemical structure of a Dibutylamide-DTPA-PM(Z) contrast agent in which Z = +2;

Figure 2 is a diagram showing the anhydride + ammonium hydroxide production of Diamide-DTPA-PM(Z) in which Z = +3;

Figure 3 is a diagram showing the anhydride + butyl amine production of Dibutylamide-DTPA-PM(Z) in which Z = +2;

Figure 4A is a colon shown in cross section (from the "Atlas of Descriptive Histology" Reith-Ross p121);

Figure 4B is a planar schematic drawing of an MR image of a colon showing surface highlighting by Diamide-DTPA-PM;

Figure 4C is a perspective schematic drawing of an MR image of a colon showing surface highlighting by Diamide-DTPA-PM of occulted and non-occulted surfaces;

Figure 5 is a cut-away perspective view of an MR system showing the motion platform and subject using Diamide-DTPA-PM paramagnetic contrast agents; and

Figure 6 is a flow chart showing a method of using the Diamide-DTPA-PM paramagnetic contrast agents.

The paramagnetic contrast agents of the present invention are amide homologs of the DTPA-PM chelate, for example having the general chemical name diamido acetyl - diethylenetriaminetriacetic acid (or

Diamide-DTPA). The probable physical chelation structure of Diamide-DTPA-PM is a classic octahedron (8 faces, 6 apexes) as shown in Figure 1A. The Diamide-DTPA homologs are strong chelators having six polar bond coordination points 104 (three nitrogen points 104:N and three oxygen points 104:0) which enclose the paramagnetic ion PM(Z) on all sides.

Diamide-DTPA-PM has the general chemical structure shown in Figure 1B. The homologs thereof have similar structures with a specific number "n" of carbons in the carbon-hydrogen portion of the amide group. The number of carbons in the methylene CH_2 chain between the -CONH-active group and the terminal methylene $-CH_3$, is "n-1".

In Diamide-DTPA-PM two of the original five acetic acid groups of DTPA have become amide groups "A". In general:

Diamide-DTPA-PM = 2A-DTPA-PM where A is a general amide group of the form:

$$A = -\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle H}{|}}{N}-(CH_2)_nH,$$

and PM is a paramagnetic metal ion. The elimination of the two carboxyl groups reduces the ion charge of the DTPA chelator from five to three.

Paramagnetic ions having a valence of Z = +3 as shown in Figure 1A and 1B, produce a diamide contrast agent of the general form:

Diamide-DTPA-PM(+3) = 2A-DTPA-PM(+3).

This type III contrast agent has a zero net charge as tabulated below:

Diamide-DTPA-PM(+3)	Charge Balance	
	2A-DTPA	PM
	(-3) +	(+3) = 0

The particle (osmolarity) to paramagnetic (molar relaxivity) ratio for Diamide-DTPA-PM(+3) type contrast agents (Z = +3) is 1:1. The Diamide-DTPA-PM(Z) contrast agents formed around paramagnetic metal ions having a charge of +3 can be prepared in highly concentrated solutions while retaining isotonicity with body fluids. The Schering DTPA-PM(+3) contrast agent has a particle to paramagnetic metal ion ratio of 3:1, and can only be made in isotonic solutions at substantially lower concentrations. Therefore, greater volumes of the Schering DTPA-PM(+3) contrast agent need be injected into animals or humans to obtain the same paramagnetic effect.

Paramagnetic ions having a valence of Z = 2, produce amide contrast agents of the general forms:

Diamide-DTPA-PM(+2), IN = 2A-DTPA-PM(+2), IN where IN is a suitable inert ion, such as a simple mineral salt cation (Na+, Li+, etc.) or an organic ion such as methyl glucamine or N-methyl glucamine, having a charge of plus one (see Figure 1C). This Type II contrast agent also has a zero net charge as tabulated below:

IN Diamide-DTPA -PM(+2)		Charge Balance
IN	2A DTPA	PM
(+1)	(-3) +	(+2) = 0

The particle to paramagnetic ratio for the Diamide-DTPA-PM(+2),IN contrast agents is 2:1, producing a low osmolarity impact.

The above Diamide-DTPA-PM Type III and Type II contrast agents have a paramagnetic effect similar to the Schering DTPA-PM contrast agent. For example, Methyl Amide DTPA-Gd(III) requires a concentration of about 3.31 mM to produce a T1 relaxation time of 67 msec (10 MHz field strength, using an RADX). The concentration of Schering DTPA-Gd(III) required to produce a similar result is about 3.16. Methyl Amide DTPA-Gd(III) has about the same paramagnetism as Schering's DTPA-Gd(III) contrast agent.

Possibly the water of hydration 108 (see Figure 1A) which collects around the amide CH_2 chains offers a reliable source of protons (H+) 110 for resonating with the applied MR fields. Protons 110 have a high probability of being present within the local magnetic field of the PM ions. These protons form a class of protons for MR imaging which is distinct from random in vivo protons. The prolonged association time of bound water 108, and the close proximity of protons 110 to the PM ion, establishes a definite and distinct T1 relaxation time which is longer than the T1 for random protons. As a result, protons 110 provided by the water of hydration appear at a higher intensity in the MR image.

A general anhydride-diamide method, as illustrated in Figures 2 and 3, is suitable for making each homolog of the amide family of Amide-DTPA-PM contrast agents. In the example below the paramagnetic ion is provided by $Fe(III)Cl_3$, for chelation into dimethylamide (n = 1). However, other paramagnetic ions in other forms may be employed for chelation into other amide homologs.

Step 1) FORMATION of Amide-DTPA (see Figure 2)
Mix 1-5 grams dianhydride DTPA (obtained from Sigma Chemical Co, St Louis MO) into 50-150 mL of 5 percent (v/v) NH_4OH (ammonium hydroxide) in water.
Fixed ratios of NaOH/DTPA are not required, Precise so long as excess NH_4OH is provided.

Step 2) HEAT the solution
for several hours (overnight) at reflux temperature
To produce the alkylamide derivative Dimethylamide-DTPA (n = 1) react instead with an alkylamine (e.g. methylamine) for example as shown in Figure 3, instead of with the NH_4OH.
Higher homologs of bisalkylamide-DTPA may be formed using the corresponding higher homolog of alkyl amines for the reactant. Chloroform may be used as the solvent for higher homologs.
Formation of the Dibutylamide-DTPA (n = 4) diamide homolog is shown in Figure 3.

Step 3) REMOVE the excess solvent,
by vacuum rotary evaporation leaving an Diamide-DTPA crystal residue.

Step 4) MIX the Diamide-DTPA residue in an $FeCl_3$ water solution of stoichiometric proportions, to form Diamide-DTPA-(Fe+3) plus 3HCL.
Type II metals will require an inert cation (IN) which may be added to the solution at this point.

Step 5) REMOVE the HCl
A) by evaporation using a rotary evaporator.
B) by neutralization using NaOH or NH_4OH.
C) by chromatogrphy using a silica gel colunm.

Step 6) REMOVE the water by vacuum-freezing to form a highly stable form of Diamide-DTPA-PM.

Step 7) DISPERSE the Amide-DTPA-PM in suitable vehicle to provide a pharmacological form.

Water is a suitable vehicle for dissolving the lower homologs of Diamide-DTPA-PM (n less than 10). Higher homologs are hydrophobic and form an emulsion with water. These higher homologs have the same density as water and therefore do not settle out. The isodense character of the homologs of Diamide-DTPA-PM permits a wide range of water:homolog ratios.

The amide family of DTPA-PM contrast agents include the homo-diamides (n = n') structure and the hetero-diamides (n not equal to n') structure.

Name of Amide	n,n'	Properties of Interest
Diamide-DTPA-PM	0,0	Excellent
Bismethylamide-DTPA-PM	1,1	renal and
Bisethylamide-DTPA-PM	2,2	blood-brain
Bispropylamide-DTPA-PM	3,3	barrier contrast
Bisbutylamide-DTPA-PM	4,4	agent.
Bispentylamide-DTPA-PM	5,5	Demonstrates renal
Bishexylamide-DTPA-PM	6,6	and hepatobiliary
Bisheptylamide-DTPA-PM	7,7	imaging.
Bisoctylamide-DTPA-PM	8,8	Also shows cardiac
Bisnonylamide-DTPA-PM	9,9	imaging of infarctions
Bisdecylamide-DTPA-PM	10,10	and ischemic lesions.
to	16,16	
Amide-Stearylamide-		Passes into the
DTPA-PM	0,18	Cardiac system imaging

The hetero-diamides may have one short CH_2 chain (n=1 or more), and one long CH_2 chain (n=18 or less). A single long hydrophobic chain, together with the charged DTPA moiety, renders the chelate an isosteric substitute for fatty acids; and produces substantial tissue levels of the chelate in these organs which have efficient fatty acid uptake systems such as the myocardium.

Venously introduced contrast agents are immediately distributed throughout the circulatory system for imaging. Organs such as the kidney, brain, liver, and heart receive substantial blood flow; and provide selective images which are agent enhanced.

Amide-DTPA-PM has a prolonged circulation time due to its high stability. The Amide-DTPA-PM contrast agent is less affected by enzyme degradation than simple ion-DTPA chelates (Schering). In addition, the higher homologs of Amide-DTPA-PM tend to be less polar and to bind more to serum proteins, further increasing their circulation time. They tend to be extracted from circulation by the liver and excreted in the hepatobiliary system. The amide contrast agent passes through the bile duct (controlled by the ampulla of Vater) and is absorbed into the colon. The Amide-DTPA-PM contrast agents are suitable for imaging the hepatobiliary (gall bladder) system.

Figure 4A is a cross sectional view of the colon 440. The biamide-DTPA-PM contrast agent appearing along the convoluted inner surface of the colon wall 442 is slowly brushed away by the luminal content 444. The high viscosity of the contrast agent prevents it from immediately mixing with the luminal content 444. Because the washout rate is slower than the excretion rate, the agent accumulates in a film or layer 446 along the inner surface of colon 440.

The paramagnetic properties of Amide-DTPA-PM enriched layer 446 establishes a shorter T1 relaxation time for the local protons within the layer. In the resulting MR image, Amide-DTPA-PM layer 446 is displayed at a higher intensity, highlighting the inner surface of the colon 440. Surface highlighted images are particularly useful in studying those disease processes involving changes in mucosal transit such as malabsorption, non-tropical sprue, ulcerative colitis and regional enteritis. The luminal content is not amide enriched and appears grey or dark (unenhanced) along with the background tissue.

Figure 4B shows a schematic MR image of the colon in cross-section, and Figure 4C shows a schematic MR image of the colon in perspective. Both simple planar views and the complex perspective views can be computer generated from the MR data. The surface amide accumulation 446 appears bright and outlines of the inner surface colon 440 unimpedded by the luminal content. This surface effect is especially noticeable in perspective view 4C which reveals the front surface 448-F, and both the unocculted back surface 448-B and occulted back surface 448-0. The thin amide layer 446 on the front surface has a transparent characteristic which permits the occulted back surface to be viewed. The display intensity of the

region of overlap between the front surface 448-F and occulted back surface 448-0 is the summation of the separate intensities.

The lower homologs tend to be more polar and remain in solution longer. These homologs are kidney selective and suitable for imaging the kidney, ureter, and bladder.

The higher homologs are fatty acid analogs and are thus extracted by the heart along with the regular fatty acids. These homologs (n = 7 and greater) are cardiac selective and suitable for imaging the cardiac system and cardiac related functions.

Oral introduction of the Diamide-DTPA-PM contrast agent requires a higher volume. The agent fills the luminal channel of the digestive system for providing a volume or bulk MR image.

The stable powder state of the Diamide-DTPA-PM contrast agents have an indefinite shelf life, and is the preferred state for shipping and storage. The contrast agent in water solution (or other solvent) is packaged in small storage vials, and frozen under a vacuum. The low pressure sublimates the solvent, leaving crystals of the contrast agent. The vial is sealed to prevent entry of external contaminants, and to to preserve the internal vacuum. The resulting freeze-dried, vacuum sealed powder, is highly stable and free from environmental degradation effects.

Prior to injection, the stable-powdered contrast agent may be raised to the pharmacological state by the addition of a suitable solvent such as water, serum, albumin solutions, or saline. A typical injectable composition contains about 10mg human serum albumin (1 percent USP Parke-Davis) and from 10 to 500 micrograms of Diamide-DTPA-PM material per milliliter of 0.01 M phosphate buffer (pH 7.5) containing 0.9 percent NaCl. The pH of the aqueous solutions may range between 5-9, preferably between 6-8. The storage vial may have twin compartments containing the desired amounts of powdered Diamide-DTPA-PM and solvent for a single application. When the seal between the compartments is broken, the Diamide-DTPA-PM goes into solution at the desired concentration for immediate use. The Diamide-DTPA-PM solution mixes readily with the in vivo fluids.

The paramagnetic species PM may be any paramagnetic element, molecule, ion or compound having a combined valence of "Z". Paramagnetic material PM includes at least one of the following elements:

Ions of Transition Elements

Cr(III)	24	(Chromium)	Co(II)	27	(Cobalt)
Mn(II)	25	(Manganese)	Ni(II)	28	(Nickel)
Fe(III)	26	(Iron)	Cu(III)	29	(Copper)
Fe(II)	26	(Iron)	Cu(II)	29	(Copper)

Ions of Lanthanide Elements

La(III)	57	(Lanthanum)	Gd(III)	64	(Gadolinium)
Ce(III)	58	(Cerium)	Tb(III)	65	(Terbium)
Pr(III)	59	(Praseodymium)	Dy(III)	66	(Dysprosium)
Nd(III)	60	(Neodymium)	Ho(III)	67	(Holmium)
Pm(III)	61	(Promethium)	Er(III)	68	(Erbium)
Sm(III)	62	(Samarium)	Tm(III)	69	(Thulium)
Eu(III)	63	(Europium)	Yb(III)	70	(Ytterbium)
			Lu(III)	71	(Lutetium)

Gd has the highest paramagnetic property; but is costly and highly toxic in the free state. Placing the Gd within the chelator produces a physiologically tolerable form of Gd; but also reduces paramagnetic effect of the Gd. The chelate structure tends to shield the paramagnetic ions and prevents close proximity to local H+ protons. Fe and Mn have a high paramagnetic property and excellent physiological tolerance. Both of these paramagnetic ions are normally present in the physiological environment.

The magnetic resonance (MR) imaging system 500, shown in Figure 5 has two magnetic components which scan subject 504 for obtaining MR data enhanced by the presence of contrast agent 508. Bulk magnetic field Mz from Z field source 510 causes paramagnetic particles such as local hydrogen protons

within the subject to align with the Z axis. Periodic or rotating field Mxy from XY field generator 514 extends between XY electrodes 516. The subject to be scanned is positioned on support platform 520 and moved through the magnetic fields by drive 522. Rotating field Mxy is tuned to cause resonant precession of the local protons within the tissue of interest. Each local proton precesses about the Z axis in response to a particular frequency of rotating field Mxy. When rotating field Mxy is removed, the precessing protons decay back into alignment with Mz.

The decay period of the local protons (spin lattice relaxation time T1) varies between organs and between conditions within the same organ. Tumor tissue tends to have a longer T1 than healthy tissue. The presence of the paramagnetic metal ions PM causes a shortening of the proton T1, without substantially affecting T2 (spin-spin relaxation time). The energy of precession is released forming a free induction signal. Grid detector 526 senses the decay signals which are stored and processed by data processer system 530, to form an image 532 on monitor 536. The metal ions in the contrast agent are not directly imaged by the MR system.

The imaging system is further disclosed in Scientific American, May 1982, pages 78-88, and "NMR A Primer for Medical Imaging" by Wolf and Popp, Slack Book Division (ISBN 0-943432-19-7), which disclosures are hereby incorporated by reference.

Figure 6 shows a method of imaging subject 504 with MR system 500 employing a paramagnetic contrast agent 508.

Step 1) PROVIDING a physiologically tolerable contrast agent 508 in the form: 2A-DTPA-(+ Z) If initially in powder form, the 2A-DTPA-PM contrast agent must be dispensed into a suitable carrier vehicle.

Step 2) INTRODUCING the 2A-DTPA-PM contrast agent into subject 508 (preferably by intravenous injection)

Step 3) WAITING for the amide functional groups to cooperate with the in vivo environment.

Step 4) IMAGING the subject with MP system 500 to obtain an enhanced MR image.

Comparison or subtraction imaging, requires an initial step of providing data from a prior MR imaging, and the final step of subtraction comparing the prior MR image with the current MR image. A historical base line image from the subjects file may be employed as the prior image. Alternatively, a current MR image made without the use of a contrast agent may be employed.

It will be apparent to those skilled in the art that the objects of this invention have been achieved as described hereinbefore by providing an improved physiologically tolerable contrast agents with a high stability, and a low toxicity. The contrast agent has a high paramagnetic effect due to the amide water of hydration, and a low osmolarity due to the amide bonding. The variability of the amide structure permits a range of vivo response and organ selection, including surface selectivity of the colon.

Claims

1. A complex of a paramagnetic polyvalent metal and an amide of diethylenetriaminepentaacetic acid in which the nitrogen of the amide group is unsubstituted or is substituted by at least one C_{1-18} alkyl radical.

2. A complex according to claim 1, wherein the metal is a lanthanide, iron, manganese, copper, cobalt, chromium or nickel.

3. A complex according to claim 1, wherein the metal is iron.

4. A complex according to claim 1, wherein the metal is manganese.

5. A complex according to claim 1, wherein the metal is gadolinium.

6. A complex according to any one of the preceding claims wherein said amide comprises diethylenetriaminepentaacetic acid wherein two of the carboxyl moieties are replaced by amide groups.

7. A complex according to any one of the preceding claims, wherein said amide group includes at least one alkyl chain of at least 7 carbons.

8. A complex according to any one of claims 1 to 6 wherein said amide group includes at least one alkyl chain having less than 10 carbon atoms.

9. A complex according to any one of claims 1 to 6 wherein said amide is the bismethylamide of diethylenetriaminepentaacetic acid.

10. A complex according to any one of claims 1 to 6 wherein said amide is the bisbutylamide of diethylenetriaminepentaacetic acid.

11. A magnetic resonance imaging contrast medium comprising a complex as claimed in any one of claims 1 to 10.

12. Use of a complex as claimed in any one of claims 1 to 10 for the manufacture of a magnetic resonance imaging contrast medium.

Revendications

1. Un complexe d'un métal polyvalent paramagnétique et d'un amide d'acide diéthylènetriaminepentaacétique, dans lequel l'azote du groupe amide est non substitué ou est substitue par au moins un radical alkyle en C_1 à C_{18}.

2. Un complexe selon la revendication 1, dans lequel le métal est un lanthanide, le fer, le manganèse, le cuivre, le cobalt, le chrome ou le nickel.

3. Un complexe selon la revendication 1, dans lequel le métal est le fer.

4. Un complexe selon la revendication 1, dans lequel le métal est le manganèse.

5. Un complexe selon la revendication 1, dans lequel le métal est le gadolinium.

6. Un complexe selon l'une quelconque des revendications précédentes, dans lequel ledit amide comprend l'acide diéthylènetriaminepentaacétique où deux des portions carboxyles sont remplacées par des groupes amides.

7. Un complexe selon l'une quelconque des revendications précédentes, dans lequel ledit groupe amide comprend au moins une chaîne alkyle d'au moins 7 carbones.

8. Un complexe selon l'une des revendications 1 à 6, dans lequel ledit groupe amide comprend au moins une chaîne alkyle ayant moins de 10 atomes de carbone.

9. Un complexe selon l'une des revendications 1 à 6, dans lequel ledit amide est le bis-méthylamide de l'acide diéthylènetriaminepentaacétique

10. Un complexe selon l'une des revendications 1 à 6, dans lequel ledit amide est le bis-butylamide de l'acide diéthylènetriaminepentaacétique.

11. Un milieu de contraste pour imagerie de résonance magnétique comprenant un complexe tel que revendiqué dans l'une quelconque des revendications 1 à 10.

12. Utilisation d'un complexe tel que revendiqué dans l'une quelconque des revendications 1 à 10 pour la fabrication d'un milieu de contraste pour imagerie de résonance magnétique.

Ansprüche

1. Ein Komplex aus einem paramagnetischen polyvalenten Metall und einem Amid der Diethylentriaminpentaessigsäure, worin der Stickstoff der Amidgruppe unsubstituiert oder mit wenigstens einem C_1-

C_{18}-Alkylrest substituiert ist.

2. Ein Komplex gemäß Anspruch 1, worin das Metall ein Lanthanid, Eisen, Mangan, Kupfer, Cobalt, Chrom oder Nickel ist.

3. Ein Komplex gemäß Anspruch 1, worin das Metall Eisen ist.

4. Ein Komplex gemäß Anspruch 1, worin das Metall Mangan ist.

5. Ein Komplex gemäß Anspruch 1, worin das Metall Gadolinium ist.

6. Ein Komplex gemäß einem der vorangehenden Ansprüche, worin das Amid Diethylentriaminpentaessigsäure umfaßt, worin zwei der Carboxylreste durch Amidgruppen ersetzt sind.

7. Ein Komplex gemäß einem der vorangehenden Ansprüche, worin die Amidgruppe wenigstens eine Alkylgruppe mit wenigstens 7 Kohlenstoffatomen umfaßt.

8. Ein Komplex gemäß einem der Ansprüche 1 bis 6, worin die Amidgruppe wenigstens eine Alkylgruppe mit weniger als 10 Kohlenstoffatomen umfaßt.

9. Ein Komplex gemäß einem der Ansprüche 1 bis 6, worin das Amid das Bismethylamid von Diethylentriaminpentaessigsäure ist.

10. Ein Komplex gemäß einem der Ansprüche 1 bis 6, worin das Amid das Bisbutylamid von Diethylentriaminpentaessigsäure ist.

11. Ein Kontrastmittel für eine magnetische Resonanz-Aufnahme, enthaltend einen Komplex gemäß einem der Ansprüche 1 bis 10.

12. Verwendung eines Komplexes gemäß einem der Ansprüche 1 bis 10 zur Herstellung eines Kontrastmittels für eine magnetische Resonanz-Aufnahme.

Figure 1A
General Diamide-DTPA(-3)PM(+3) Molecule
Probable Chelate Structure

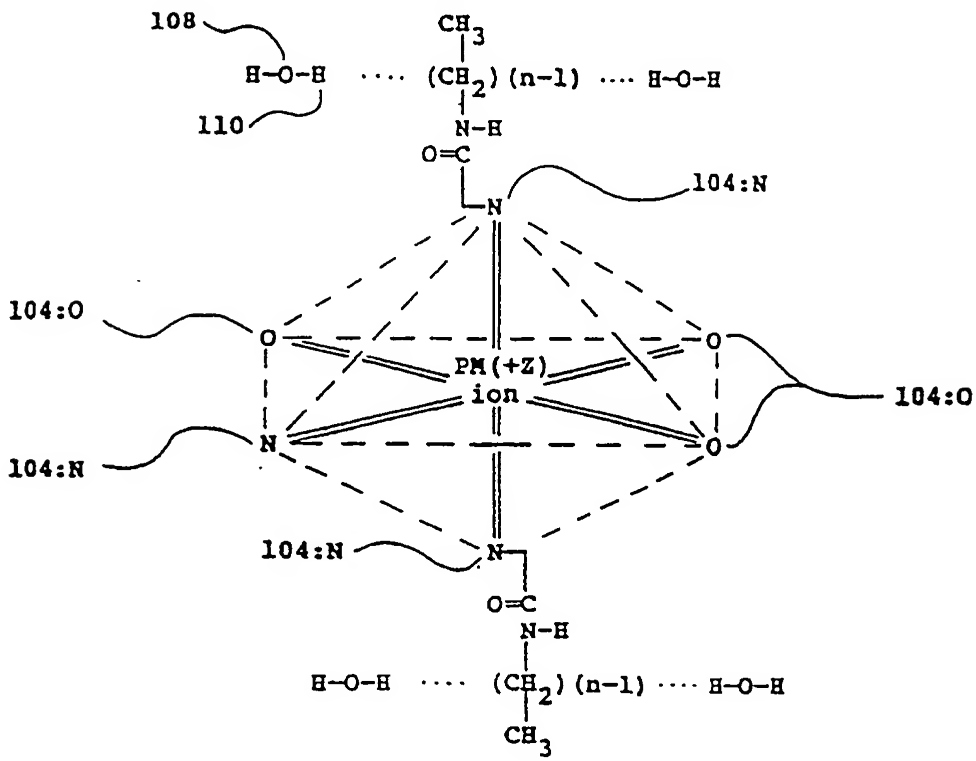


Figure 1B
Diamide-DTPA(-3)PM(+3) Molecule
(diamido acetyl diethylenetriaminetriacetic acid)

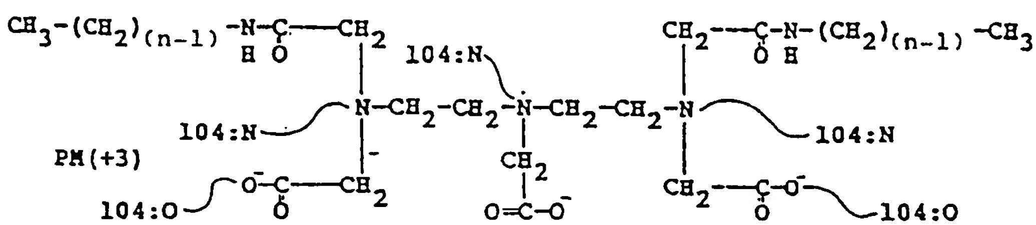


Figure 1C
Dibutyl amide DTPA(-3)PM(+2) IN(+) Molecule
(dibutylamido acetyl diethylenetriaminetriacetic acid)

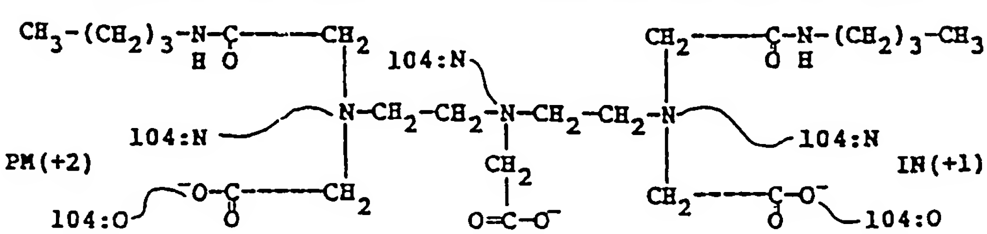
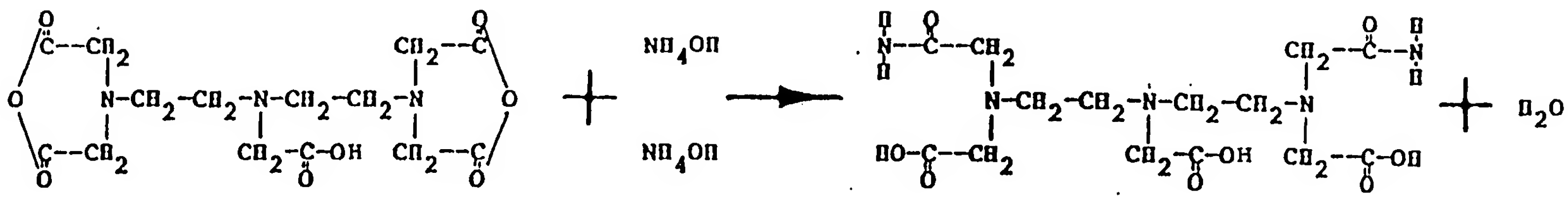
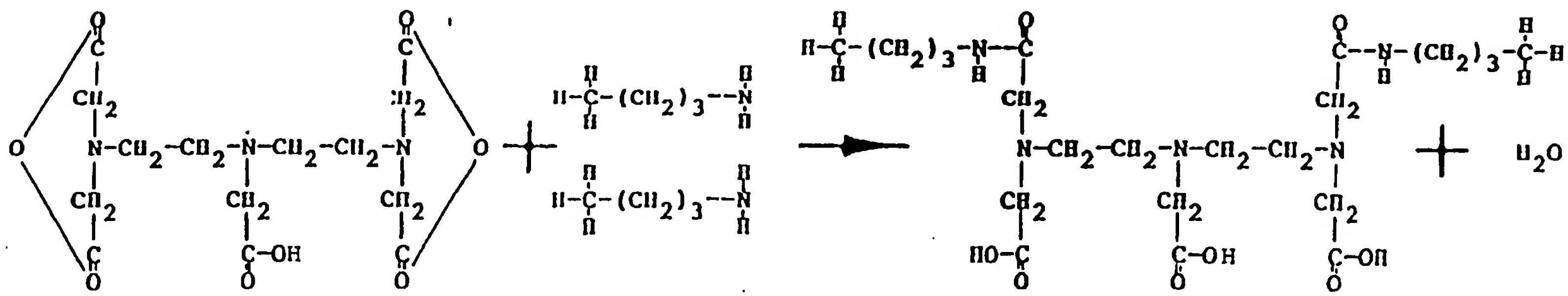


Figure 2
Formation of Diamide-DTPA



Dianhydride DTPA plus Ammonium Hydroxide yields Diamide-DTPA plus Water

Figure 3
Formation of Dibutyl Amide DTPA



Dianhydride DTPA plus Butyl Amine yields Dibutyl Amide DTPA plus Water

FIGURE 4A
COLON CROSS SECTION

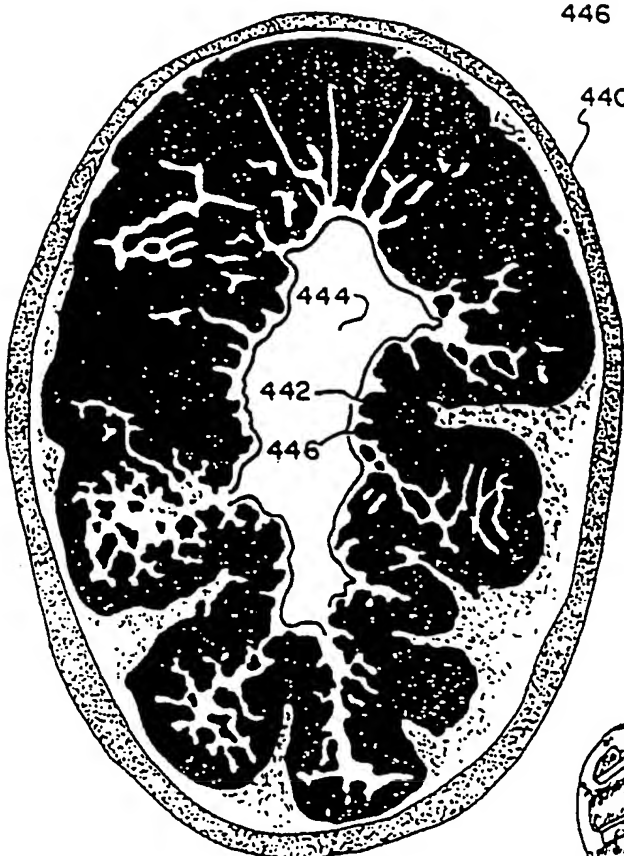


FIGURE 4B
COLON SCHEMATIC
CROSS SECTION

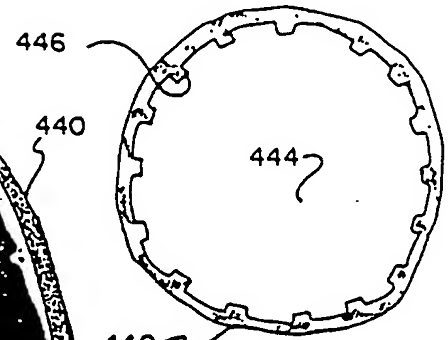


FIGURE 4C
COLON SCHEMATIC
PERSPECTIVE

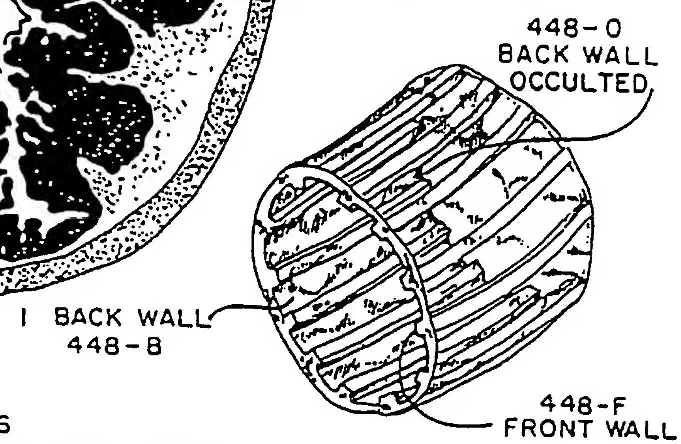


FIGURE 6
METHOD OF USING CONTRAST AGENT
AMIDE-DTPA-PM

STEP 1 PROVIDING CONTRAST AGENT AMIDE-DTPA-PM

STEP 2 INTRODUCING CONTRAST AGENT INTO SUBJECT

STEP 3 WAITING FOR IN VIVO COOPERATION

STEP 4 IMAGING SUBJECT TO OBTAIN ENHANCED IMAGE

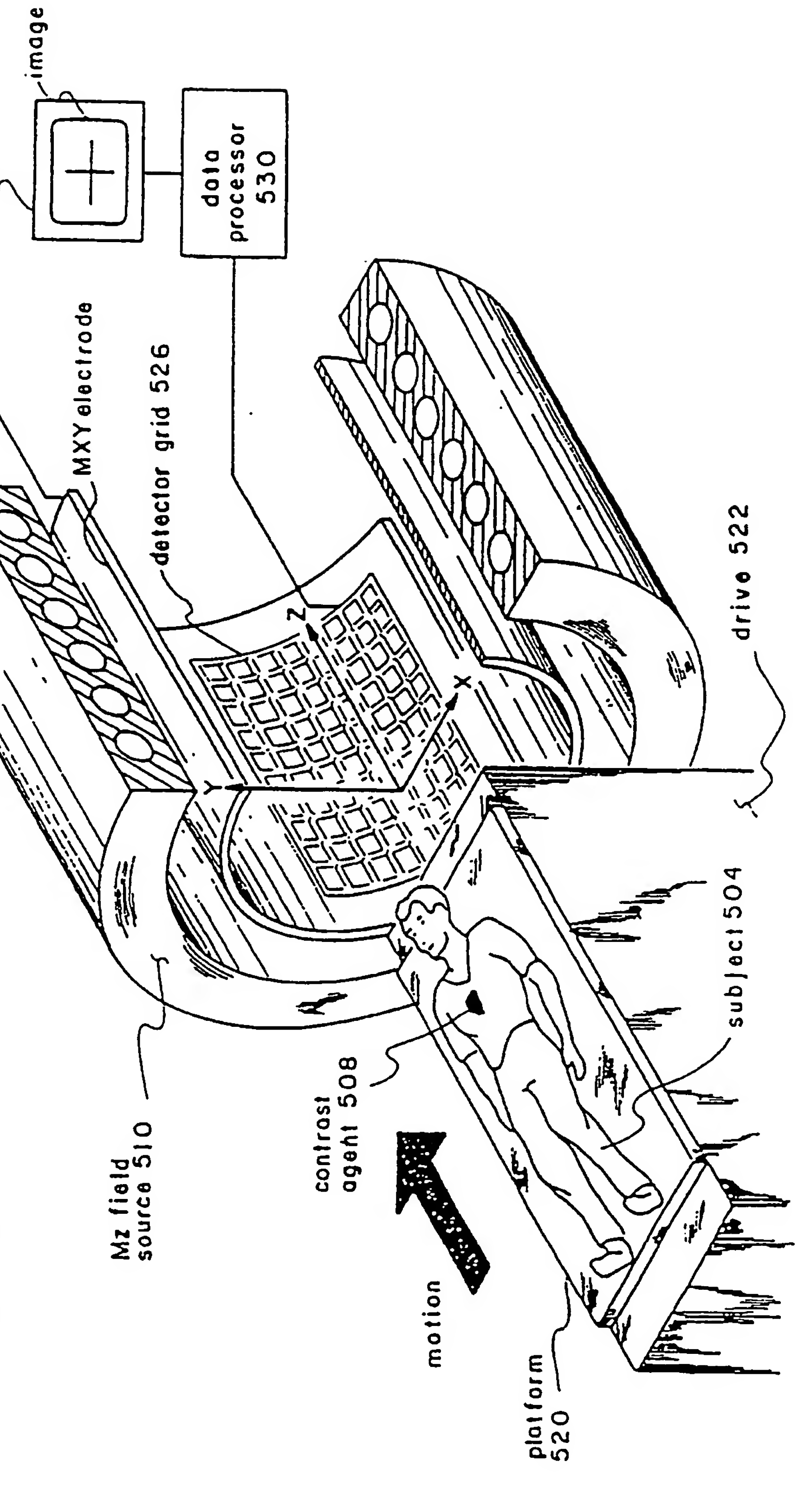


FIG. 5
MRI System 500